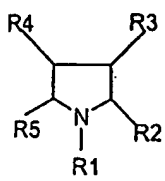




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(21) International Application Number: PCT/DK00/00055 (22) International Filing Date: 10 February 2000 (10.02.00) (30) Priority Data: PA 1999 00188 12 February 1999 (12.02.99) DK (71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK). (72) Inventors: STURIS, Jeppe; Åkandevej 60, DK-3500 Vær- løse (DK). KRISTIANSEN, Marit; Gustav Esmanns Allé 2, DK-2860 Søborg (DK). BJERNING, Christina; Kirse- bærvangen 81, DK-2765 Smørum (DK).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: USE OF PYRROLIDINE DERIVATIVES FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OR PROPHYLAXIS OF OBESITY OR APPETITE REGULATION <div style="text-align: center;">  <div style="margin-left: 100px;">(I)</div> </div> (57) Abstract The present invention relates to the use of compounds of general formula (I) for the treatment or prophylaxis of obesity or appetite regulation. The present invention also embraces use of glycogen phosphorylase inhibitors for the treatment or prophylaxis of obesity or appetite regulation and methods of using the compounds and their pharmaceutical compositions.		

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Use of pyrrolidine derivatives for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of obesity or appetite regulation.

FIELD OF THIS INVENTION

5 The present invention relates to the use of compounds of the general formula I for the treatment or prophylaxis of obesity or appetite regulation. The present invention also embraces use of glycogen phosphorylase inhibitors for the treatment or prophylaxis of obesity or appetite regulation and methods of using the compounds and their pharmaceutical compositions.

10 BACKGROUND OF THIS INVENTION

Obesity is a well-known risk factor for the development of many very common diseases such as atherosclerosis, hypertension and diabetes. The incidence of obese people and thereby also these diseases is increasing throughout the entire industrialised world.

Due to its indirect but important effect as a risk factor in mortal and common diseases it will
15 be important to find treatment for obesity or appetite regulation.

Exercise, diet modification and food restriction will reduce body weight but for most patients, this is not feasible. Pharmacological treatment available up to date only consists of Sibutramine (acting via serotonergic mechanisms, Knoll Pharm) and Orlistat (reducing fat uptake
20 from the gut, Roche Pharm) neither reducing body weight effectively nor acceptably.

The term obesity implies an excess of adipose tissue. In this context obesity is best viewed as any degree of excess adiposity that imparts a health risk. The cut off between normal and obese individuals can only be approximated, but the health risk imparted by the obesity is probably a continuum with increasing adiposity. The Framingham study demonstrated that a
25 20% excess over desirable weight clearly imparted a health risk. (Mann GV N.Engl.J.Med 291:226, 1974). In the United States a National Institutes of Health consensus panel on obesity agreed that a 20% increase in relative weight or a body mass index (BMI = body weight in kilograms divided by the square of the height in meters) above the 85th percentile for young adults constitutes a health risk. By the use of these criteria 20 to 30 percent of adult
30 men and 30 to 40 percent of adult women in the United States are obese. (NIH, Ann Intern Med 103:147, 1985).

Indeed, the prevalence of obesity has increased with 100% in most western countries the last 20 years, and this is very serious because even mild obesity increases the risk for premature death, type 2 diabetes, coronary heart disease, hypertension, atherosclerosis, sleep
35 apnea and respiratory problems, osteoarthritis gallbladder disease and certain types of can-

cer (endometrial, breast, prostate and colon. Because of the high prevalence of obesity and its health consequences, its prevention and treatment should be a high public health priority. When energy intake exceeds expenditure, the excess calories are stored in adipose tissue, and if this net positive balance is prolonged, obesity results, i.e. there are two components to weight balance, and an abnormality on either side (intake or expenditure) can lead to obesity.

The regulation of feeding behaviour is incompletely understood. Certain is that brain neurochemicals located in specific hypothalamic nuclei regulate onset and termination of feeding. Several regulatory processes may influence these hypothalamic centres: *Metabolic signals* such as postprandial increases in plasma glucose and insulin; meal-induced *gastric distension* is another possible inhibitory factor. *Local control* by brain neurochemicals and catecholamines/beta3-adrenoceptors (inhibits feeding and stimulates energy expenditure). Psychological, social, and genetic factors also influence food intake.

At present a variety of techniques are available to effect initial weight loss. Unfortunately, initial weight loss is not an optimal therapeutic goal. Rather, the problem is that most obese patient eventually regain their weight. An effective means to establish and/or sustain weight loss is the major challenge in the treatment of obesity today.

Thus there remains today a need in the art for compositions and methods that are useful for the treatment or prophylaxis of obesity or appetite regulation.

One object of the present invention is to provide compounds which can effectively be used for the treatment or prophylaxis of obesity or appetite regulation.

BRIEF DESCRIPTION OF THIS INVENTION

Surprisingly, it has now turned out that administration of compounds that are a glycogen phosphorylase inhibitors has an effect on food intake, specifically the intake of food with a high content of fat, satiety, appetite and weight disorders. Based on these observations it is now possible to provide a medicament and a method for the treatment or prophylaxis of obesity or appetite regulation.

DETAILED DESCRIPTION OF THIS INVENTION

Glycogen phosphorylase inhibitors constitute a class of compounds which have use in the treatment of diabetes mellitus.

Substituted N-(indole-2-carbonyl)-glycinamides acting as glycogen phosphorylase inhibitors are disclosed in PCT-publication No. WO96/39384, WO96/39385 and in EP-A-0 846 464, all hereby incorporated by reference. Piperidine and pyrrolidine compounds acting as glycogen phosphorylase inhibitors are disclosed in PCT-publication No. WO 95/24391, WO 97/09040,
5 WO98/40353 and WO 98/50359, all hereby incorporated by reference.

International patent application having publication No. WO 97/09040 relates to (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine and other substituted 2-alkylpyrrolidines and their use for treatment of diabetes.

10

Any glycogen phosphorylase inhibitor may be used as a compound (active agent) of this invention. Such inhibitors can readily be determined by those skilled in the art.

15

Phosphorylase can either be purchased from Sigma or extracted from rat livers according to Stalmans et. al. (Eur.J.Bio-chem. 49 (1974), 415). The activity of phosphorylase can be determined as described by Bergmeyer (1983; in: Meth. of Enzymatic Analysis, 2, 293-295, Weinheim, (ed.) Verlag Chemie). A compound is considered to be a potent glycogen phosphorylase inhibitor if the IC₅₀ value is less than 10 μ M. A variety of glycogen phosphorylase inhibitors are described above, however, other glycogen phosphorylase inhibitors will be known to those skilled in the art, such as 1-[N-(5-chloroindole-2-carbonyl)-3-(4-fluorophenyl)-L-Alanyl]-4-hydroxypiperidine and (3R,4R,5R)-5-hydroxymethyl-3,4-piperidinediol.
20

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The present invention is based in part on the discovery that a representative glycogen phosphorylase inhibitor, 2-alkylpyrrolidine, (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine is effective in appetite regulation and against obesity, in Sprague Dawley rats and in Zucker Diabetic Fatty (ZDF) rats. ZDF rats are generally recognised models of hyperphagia, obesity and diabetes.

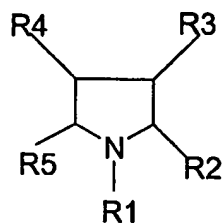
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These data thus indicate that glycogen phosphorylase inhibitors and the 2-alkylpyrrolidine of formula I are useful as therapeutic appetite regulation agents and therapeutic agent against obesity in mammals, including primates such as humans.

35

The present invention is furthermore useful in treatment or prophylaxes of diseases where lowering of the lipid content in the blood is beneficial such as dyslipidemia, hypertriglyceridemia, hyperlipidemia, hyperlipoproteinaemia, cardiovascular diseases and hypertension.

The present invention provides the use of a compound of the general formula (I)



(I)

wherein R¹ is hydrogen, acyl, alkene, cycloalkyl or alkyl which optionally is substituted with one or more of the following groups: hydroxy, alkoxy, amino, N-alkylamino, N,N-dialkylamino, halogen, cycloalkyl, optionally substituted phenyl or alkoxycarbonyl, R² is hydrogen or alkyl, R³ and R⁴, which are the same or different, independent of each other, is hydrogen, halogen, hydroxy, mercapto or amino which is optionally substituted with alkyl or aralkyl, and R⁵ is alkyl substituted with hydroxy, halogen, amino, N-alkylamino, N,N-dialkylamino or mercapto, or pharmaceutically acceptable salts or hydrates thereof including any of the optical isomers or mixtures thereof, for the manufacture of a medicament for the treatment or prophylaxis of obesity or appetite regulation.

Hereinafter, the term alkyl, when used alone or in combination with another moiety, is a straight or branched saturated hydrocarbon chain group which preferably contains not more than 8 carbon atoms, more preferred not more than 4 carbon atoms. Especially preferred alkyl groups are methyl, ethyl, propyl and isopropyl.

The term halogen as used herein refers to chloro, bromo or fluoro, preferably fluoro. Preferably, N-alkylamino is N-methylamino. Preferably, N,N-dialkylamino is N,N-dimethyl-amino. The term acyl as used herein refers to carbonyl substituted with hydrogen, alkyl or phenyl. Herein, cycloalkyl preferably contains 3-7 carbon atoms, more preferred 3-6 carbon atoms. Alkoxy preferably is methoxy or ethoxy. Alkoxycarbonyl preferably is methoxycarbonyl or ethoxycarbonyl. Aralkyl preferably is benzyl. Trifluoroalkyl preferably is trifluoromethyl or 2,2,2-trifluoroethyl. Alkene preferably contains not more than 8 carbon atoms and preferably is allyl. The term "one or more" substituents preferably is 1-3 substituents, most preferred 1.

In one embodiment compound of formula (I) contains at least 2 hydroxy groups in another embodiment formula (I) contains at least 3 hydroxy groups.

A subgroup of compounds to be used according to this invention are compounds of formula I wherein the two substituent designated by the symbols R3 and R5 are situated at the same side of the plane formed by the 5 membered nitrogen containing ring, and R4 is situated at the opposite side of the plane formed by the 5 membered nitrogen containing ring.

5

Examples of compounds to be used according to this invention are compounds of formula I wherein R1 is alkyl which optionally is substituted with one or more of the following groups: hydroxy, alkoxy, amino, N-alkylamino, N,N-dialkylamino, alkoxycarbonyl, cycloalkyl or optionally substituted phenyl.

10

In one embodiment R1 is hydrogen.

Another example of compounds to be used according to this invention are compounds of formula I wherein R1 is phenylalkyl wherein the phenyl moiety optionally is substituted with one or more of the following groups: halogen, hydroxy, alkoxy, trifluoromethyl or cyano.

15

In another embodiment R3 and R4 are both hydroxy.

In still another embodiment R5 is hydroxyalkyl, such as hydroxymethyl.

20

Another subgroup of compounds to be used according to this invention are compounds of formula I wherein R3 and R4 each are hydroxy, and R5 is hydroxymethyl.

Any possible combination of two or more of the embodiment described herein is comprised within the scope of the present invention.

25

The compounds of formula I may be presented as a mixture of isomers which, if desired, may be resolved into the individual pure enantiomers. This resolution may conveniently be performed by fractional crystallisation from various solvents, of the salts of compounds of the formula I with optical active acids or by other methods known per se, for example, chiral column chromatography. This invention includes all isomers, whether resolved or mixtures thereof.

30

Examples of compounds to be used according to this invention are 3,4-dihydroxy-2-hydroxymethylpyrrolidine, 3,4-dihydroxy-2-hydroxymethyl-1-methylpyrrolidine, 1-cyclopropylmethyl-3,4-dihydroxy-2-hydroxymethyl-pyrrolidine, 3,4-dihydroxy-2-

35

hydroxymethyl-1-propylpyrrolidine, 1-butyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, 3,4-dihydroxy-2-hydroxymethyl-1-(2,2,2-trifluoroethyl)pyrrolidine, 1-benzyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, 3,4-dihydroxy-2-hydroxymethyl-1-(2-hydroxyethyl)pyrrolidine, 3,4-dihydroxy-2-hydroxymethyl-1-(1,3-dihydroxyprop-2-yl)pyrrolidine, 3,4-dihydroxy-2-hydroxymethyl-1-(2,3-dihydroxyprop-1-yl)pyrrolidine, 1-(2-aminoethyl)-3,4-dihydroxy-2-hydroxymethylpyrrolidine and salts and hydrates thereof, preferably (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethyl-1-methylpyrrolidine, (2R,3R,4R)-1-cyclopropylmethyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethyl-1-propylpyrrolidine, (2R,3R,4R)-1-butyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethyl-1-(2,2,2-trifluoroethyl)pyrrolidine, (2R,3R,4R)-1-benzyl-3,4-dihydroxy-2-hydroxy-methylpyrrolidine, (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethyl-1-(2-hydroxyethyl)pyrrolidine, (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethyl-1-(2,3-di-hydroxy-prop-1-yl)pyrrolidine, (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethyl-1-(1,3-dihydroxy-prop-2-yl)pyrrolidine, (2R,3R,4R)-1-(2-aminoethyl)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2S,3S,4S)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2S,3S,4S)-3,4-dihydroxy-2-hydroxymethyl-1-methylpyrrolidine, (2S,3S,4S)-1-cyclopropylmethyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2S,3S,4S)-3,4-dihydroxy-2-hydroxy-methyl-1-propyl-pyrrolidine, (2S,3S,4S)-1-butyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2S,3S,4S)-3,4-dihydroxy-2-hydroxymethyl-1-(2,2,2-trifluoroethyl)pyrrolidine, (2S,3S,4S)-1-benzyl-3,4-dihydroxy-2-hydroxymethyl-pyrrolidine, (2S,3S,4S)-3,4-dihydroxy-2-hydroxymethyl-1-(2-hydroxyethyl)pyrrolidine, (2S,3S,4S)-3,4-dihydroxy-2-hydroxymethyl-1-(2,3-dihydroxyprop-1-yl)pyrrolidine, (2S,3S,4S)-3,4-dihydroxy-2-hydroxymethyl-1-(1,3-dihydroxyprop-2-yl)pyrrolidine, (2S,3S,4S)-1-(2-aminoethyl)-3,4-dihydroxy-2-hydroxymethylpyrrolidine and salts and hydrates thereof.

25

In one embodiment the compound of general formula (I) is (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, hydrochloride or (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, hydrobromide.

30

In a further aspect, the present invention relates to (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, hydrobromide.

In a further aspect, the present invention relates to the use of a compound of formula (I) for the manufacture of a medicament for lowering of food intake.

35

In one embodiment, the present invention relates to the use of (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine for the manufacture of a medicament for lowering of food intake.

5 In another embodiment, the present invention relates to the use of a glycogen phosphorylase inhibitor for the manufacture of a medicament for lowering of food intake.

In a further aspect, the present invention relates to the use of a compound of formula (I) for the manufacture of a medicament for lowering of food intake of food with a high fat content.

10 In one embodiment, the present invention relates to the use of (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine for the manufacture of a medicament for lowering of food intake of food with a high fat content.

15 In another embodiment, the present invention relates to the use of a glycogen phosphorylase inhibitor for the manufacture of a medicament for lowering of food intake of food with a high fat content.

20 In a further aspect, the present invention relates to the use of a compound of formula (I) for the manufacture of a medicament for changing the preference of food with a high fat content to food with a low fat content.

25 In one embodiment, the present invention relates to the use of (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine for the manufacture of a medicament for changing the preference of food with a high fat content to food with a low fat content.

In another embodiment, the present invention relates to the use of a glycogen phosphorylase inhibitor for the manufacture of a medicament for changing the preference of food with a high fat content to food with a low fat content.

30 In still a further aspect, the present invention relates to the use of a glycogen phosphorylase inhibitor for the manufacture of a medicament for the treatment or prophylaxis of obesity or appetite regulation.

35 In one embodiment, the present invention relates to the use of a glycogen phosphorylase inhibitor with an IC₅₀ value less than 10 μ M.

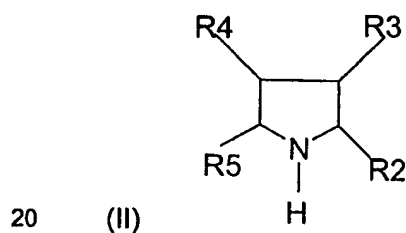
In still a further aspect, the present invention relates to a method for the treatment or prophylaxis of obesity or appetite regulation which method comprises administering an effective amount of a compound of formula I defined in anyone of the preceding claims to a patient in need of such a treatment.

- 5 In still a further aspect, the present invention relates to a method for the treatment or prophylaxis of obesity or appetite regulation which method comprises administering an effective amount of a glycogen phosphorylase inhibitor to a patient in need of such a treatment.

10 Generally, the compounds of formula I are prepared by methods known per se by the skilled art worker, for example as described in the following. The compounds of formula I can be prepared by joining the C-1 and C-4 of xylose together with nitrogen to form the pyrrolidine ring as described in Tetrahedron 42 (1986), 5685 et seq, hereby incorporated by reference. A variety of functional groups can be introduced in the compounds prepared as out-lined above by methods well known to those skilled in the art.

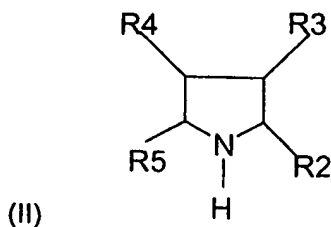
15 More specifically, the compounds of formula I can be prepared as follows:

a) Reacting a compound of the general formula II



wherein R2, R3, R4, and R5 are as defined in the claims below, with an aldehyde in presence of a reducing agent among which sodium cyanoborohydride is preferred, to form a compound of formula I.

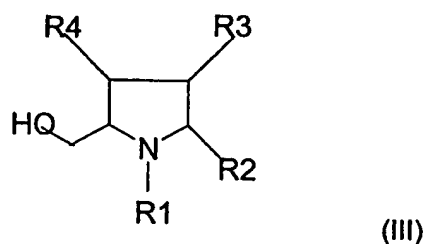
25 b) Reacting a compound of the general formula II



wherein R2, R3, R4, and R5 are as defined in the claims below, with a compound of the general formula R1Y, wherein R1 is as defined in the claims below, and Y is a leaving group, to form a compound of formula I. The reaction is carried out under alkaline conditions, i.e. in the presence of a base.

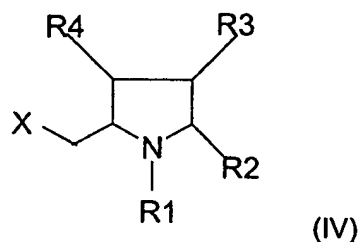
The leaving group, Y, may be any suitable leaving group as for example halogen.

c) Reacting a compound of the general formula III



wherein R1 either is as defined in the claims below or is a readily removable protection group, i.e. benzyl, R2 is as defined in the claims below and R3 and R4 are protected hydroxy, i.e. benzyloxy, with a halogenating agent such as thionyl chloride, thionyl bromide, or diethylaminosulfur trifluoride (DAST) and subsequent removal of the protection groups to form a compound of formula I, wherein R1, R3, and R4 are as defined in the claims below, and R5 is methyl substituted with halogen.

d) Reacting a compound of the general formula IV

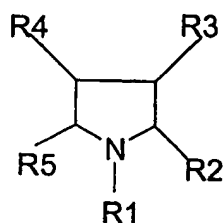


wherein R1 either is as defined in the claims below or is a readily removable protection group, i.e. benzyl, R2 is as defined in the claims below, R3 and R4 are protected hydroxy, i.e. benzyloxy, and X is a leaving group, with a compound of the general formula NHR6R7, wherein the two substituents R6 and R7 may both be alkyl, or one is alkyl and the other is hydrogen or together with NH R6 and R7 form phthalimide, and subsequent removal of the

protection groups to form the compounds of formula I, wherein R1, R2, R3, and R4 are as defined in the claims below, and R5 is methyl substituted with amino, N-alkylamino, or N,N-dialkylamino.

- 5 The leaving group, X, may be any suitable leaving group as for example halogen.

e) Reacting a compound of the general formula I



(I)

10 wherein R1 and R2 are as defined in the claims below, and one or two of the groups R3 and R4 is hydroxy and the remaining is protected hydroxy, i.e. benzyl, R5 is as defined in the claims below or is a corresponding protected group, with a halogenating agent such as thionyl chloride, thionyl bromide or diethylaminosulfur trifluoride (DAST) and subsequent removal
15 of the protection groups to form a compound of the formula I, wherein R1, R2 and R5 are as defined in the claims below, and R3 and R4 are hydroxy or halogen, but not more than one of R3 and R4 is hydroxy.

20 PHARMACEUTICAL COMPOSITION

Examples of pharmaceutically acceptable salts are acid addition salts with non-toxic acids, either inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid, or organic acids such as formic acid, acetic acid, propionic acid, succinic
25 acid, gluconic acid, lactic acid, citric acid, ascorbic acid, benzoic acid, embonic acid, methanesulphonic acid and malonic acid.

2-alkyl-pyrrolidines of formula I and their salts are useful within human and veterinary medicine, for example, in the treatment of patients suffering from obesity. For use within the present invention, 2-alkyl-pyrrolidines of formula I and their pharmaceutically acceptable salts
30 are formulated with a pharmaceutically acceptable carrier to provide a medicament for parenteral, oral, nasal, rectal, subdermal or intradermal or transdermal, pulmonal, buccal administration according to conventional methods. Formulations may further include one or

more diluents, fillers, emulsifiers, preservatives, buffers, excipients, etc. and may be provided in such forms as liquids, powders, emulsions, suppositories, liposomes, transdermal patches, controlled release, dermal implants, tablets, etc. One skilled in this art may formulate the compounds of formula I in an appropriate manner, and in accordance with accepted practices, such as those disclosed in Remington's Pharmaceutical Sciences, Gennaro, ed., Mack Publishing Co., Easton, PA, 1990.

Oral administration is preferred. Thus, the active compound of formula I is prepared in a form suitable for oral administration, such as a tablet or capsule. Typically, a pharmaceutically acceptable salt of the compound of formula I is combined with a carrier and moulded into a tablet. Suitable carriers in this regard include starch, sugars, dicalcium phosphate, calcium stearate, magnesium stearate and the like. Such compositions may further include one or more auxiliary substances, such as wetting agents, emulsifiers, preservatives, stabilizers, colouring additives, etc.

Pharmaceutical compositions containing a compound of formula I may be administered one or more times per day or week. An effective amount of such a pharmaceutical composition is the amount that provides a clinically significant effect against obesity or appetite regulation. Such amounts will depend, in part, on the particular condition to be treated, age, weight, and general health of the patient, and other factors evident to those skilled in the art. A convenient daily dosage can be less than about 1g, preferably in the range around 50-1000mg.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection.

The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

EXAMPLES

Example 1

Test 1

The effects of oral administration of (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, herein referred to as compound 1, on food intake and weight gain have been examined in the male Zucker diabetic fatty (ZDF) rat, a genetic model of obesity, insulin resistance and Type 2 diabetes. Twenty male ZDF rats were acquired from Genetic Models Inc., Indianapolis Indiana,

USA. At ten weeks of age the animals were orally dosed with either compound 1 (n=10) or vehicle (n=10). Compound was administered in the drinking water to which the animals had continuous access. Animals were caged in groups of five, i.e. two cages were treated with compound 1 and two cages were treated with vehicle.

5

	Body weight (g)	Unfasted blood glucose (mM)
Compound 1 group (n=10)	332±19	14.2±3.8
Vehicle group (n=10)	336±17	14.2±3.6

Table 1. Body weight and unfasted glucose in the two groups prior to administration of any compound 1. Data are expressed as mean±SD.

Initial body weights and unfasted glucose levels were not different between the two groups (Table 1). During seven days of therapy (mean drug administration in the compound 1 treated group being 171 mg/kg/24h), food intake was markedly reduced in the drug-treated group. Thus, the average daily food intake during the seven days for all animals in each group was 18% lower in the group treated with compound 1 than in the vehicle treated group (160±10 vs 196±13 g chow/cage/24h, $p<0.05$ by repeated measures ANOVA). The lower food intake was associated with a significantly smaller increase in body weight in the animals treated with compound 1 than in vehicle treated animals (28.1±4.5 g/rat vs 32.9±3.4 g/rat, $p<0.02$). No deleterious toxicological effects were observed in this study.

Test 2

Twenty-eight genetically obese male Zucker fatty (fa/fa) rats are bought from Charles River, Germany. The animals are housed in metal hanging cages in groups of 3 or 4 per cage and have ad libitum access to food and water for one week of acclimation. Room temperature is maintained at $21\pm 0.5^{\circ}\text{C}$ with a relative humidity of 40%. The photoperiod in the room is 12 hours light and 12 hours dark.

25

After a one week acclimation period dosing with the test compounds is initiated. The amount of compound administered is from 0.001 to 100 mg/day and the period of administration is 1 month. The compound is given by gavage twice daily. The food consumption is measured daily and the animals are weighed two times per week during the treatment period.

30

Test 3

The same procedure is used as in Test 2, except the period of administration is 3 months.

Test 4

The same procedure is used as in Test 2, except the period of administration is 6 months.

Test 5

- 5 Between 3 and 20 obese (according to the criteria mentioned above) women are administered a compound of the present invention. The amount of compound administered is from 0.1 to 4000 mg/day, and the period of treatment is 6 months.

10 The women are observed during the period of administration, and up to 3 months after discontinuance of administration, for effects on their obesity.

Test 6

The same procedure is used as in Test 5, except the period of administration is 1 year.

Test 7

15 The same procedure is used as in Test 5, except between 3 and 20 obese males are used.

Test 8

20 The same procedure is used as in Test 7, except the period of administration is 1 year.

Example 2**Test 9**

The effects of intraperitoneally (i.p.) administration of (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, herein referred to as compound 1, on food intake and weight gain have been examined in the male Sprague-Dawley rats.

25 Thirty male Sprague-Dawley rats aged 10 week were allocated into four groups: group A (n=5) and group B (n=10) were placed on a high-fat diet and group C (n=5) and group D (n=10) were placed on a high-carbohydrate diet (High-fat diet Bio-Serv, diet#F3730, 40% fat; 36% carbohydrates; High-carbohydrate diet Bio-Serv, diet#F3729 4.9% fat, 57% carbohydrates).

30 After a four-day baseline period, groups A and C were administered intraperitoneal (i.p.) twice daily for seven days with 85 mg/kg/dose of compound 1, while groups B and D were administered intraperitoneal twice daily for seven days with vehicle. During the treatment period, food intake was significantly lower during compound 1 administration in group A compared to group B while there was no difference in food intake between group C and D.

35 Accordingly, a significantly smaller increase in body weight was observed in group A vs Group B, while no difference in body weight increase was observed between groups C and

D. In the tables below food intake and body weights on the final day of treatment are summarized (mean \pm SEM).

	Food intake (g chow)	Body weight (g)
Group A	20.8 \pm 2.3*	376 \pm 15*
Group B	26.1 \pm 1.9	411 \pm 7

5 *p<0.05 vs Group B

	Food intake (g chow)	Body weight (g)
Group C	25.4 \pm 1.6*	386 \pm 11*
Group D	27.0 \pm 1.8	395 \pm 10

*not significant vs Group D

10 These data strongly imply that if animals are given a choice of high-fat and high-carbohydrate foods, compound 1 cause a shift in food preference, resulting in a reduced fat intake, a relatively increased carbohydrate intake, and an overall reduction in caloric intake and a lower body weight compared to vehicle. To show this experimentally, the following experiment can be performed:

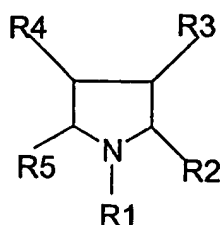
15 Test 10:

Twenty male Sprague-Dawley rats are allocated into two groups and are presented with a high-fat diet ad libitum. After a two week acclimation period, the animals are presented with an isocaloric, high-carbohydrate diet as well as. During the following two baseline weeks, the consumption of the two types of foods is measured on a daily basis. Hereafter, one group is injected intraperitoneally twice daily for seven days with 85 mg/kg/dose compound 1, the other group is injected intraperitoneally twice daily with vehicle. The consumption of the two types of foods and the change in body weight is measured and compared between the groups and between treatment and baseline periods. Based on the results in the previous example, treatment with compound 1 will cause the animals to eat less high fat food, relatively more high carbohydrate food, fewer total calories as well as a reduction in body weight, all relative to the vehicle treated group.

CLAIMS

1. The use of a compound of the general formula (I)

5



(I)

- 10 wherein R¹ is hydrogen, acyl, alkene, cycloalkyl or alkyl which optionally is substituted with one or more of the following groups: hydroxy, alkoxy, amino, N-alkylamino, N,N-dialkylamino, halogen, cycloalkyl, optionally substituted phenyl or alkoxycarbonyl, R² is hydrogen or alkyl, R³ and R⁴, which are the same or different, independent of each other, is hydrogen, halogen, hydroxy, mercapto or amino which is optionally substituted with alkyl or aralkyl, and
15 R⁵ is alkyl substituted with hydroxy, halogen, amino, N-alkylamino, N,N-dialkylamino or mercapto,
or pharmaceutically acceptable salts or hydrates thereof including any of the optical isomers or mixtures thereof,
for the manufacture of a medicament for the treatment or prophylaxis of obesity or appetite
20 regulation.

2. The use, according to claim 1, wherein the compound of formula (I) contains at least 2 hydroxy groups.

- 25 3. The use, according to claim 1, wherein the compound of formula (I) contains at least 3 hydroxy groups.

4. The use, according to any one of the claims 1 to 3, wherein R³ and R⁵ are situated at the same side of the plane formed by the 5-membered nitrogen containing ring, and R⁴ is

situated at the opposite side of the plane formed by the 5-membered nitrogen containing ring.

5. The use, according to any one of the claims 1-4, wherein R^1 represents hydrogen,
5 acyl or alkyl which is optionally substituted with one or more of the following groups: hydroxy, alkoxy, amino, N-alkylamino, N,N-dialkylamino, phenyl or alkoxycarbonyl.

6. The use, according to any one of the claims 1 to 5, wherein R^1 is methyl.

10 7. The use, according to any of one of the claims 1 to 4, wherein R^1 is hydrogen.

8. The use, according to any one of the claims 1 to 7, wherein the optionally substituted phenyl group is phenyl substituted with one or more of the following groups: halogen, hydroxy, alkoxy, trifluoroalkyl or cyano.

15

9. The use, according to any one of the claims 1 to 8, wherein R^2 is methyl.

10. The use, according to any one of the claims 1 to 8, wherein R^2 is hydrogen.

20 11. The use, according to any one of the claims 1 to 10, wherein R^3 is hydrogen, hydroxy, halogen or amino.

12. The use, according to any one of the claims 1-11, wherein R^3 is hydroxy or halogen, preferably fluoro.

25

13. The use, according to any one of the claims 1-12, wherein R^3 is hydroxy.

14. The use, according to any one of the claims 1-13, wherein R^4 is hydrogen, hydroxy, halogen or amino.

30

15. The use, according to any one of the claims 1-14, wherein R^4 is hydroxy or halogen preferably fluoro.

16. The use, according to any one of the claims 1-15, wherein R^4 is hydroxy.

17. The use, according to any one of the claims 1-16, wherein in the compound of formula I R^5 is hydroxyalkyl.

5 18. The use, according to any one of the claims 1-17, wherein R^5 is hydroxymethyl, hydroxyethyl or hydroxypropyl, preferably hydroxymethyl.

19. The use, according to any one of the claims 1-16, wherein R^5 is hydroxymethyl.

10 20. The use according to claim 1, wherein the compound of general formula (I) is 3,4-dihydroxy-2-hydroxymethylpyrrolidine, 3,4-dihydroxy-2-hydroxymethyl-1-methylpyrrolidine, 1-cyclopropylmethyl-3,4-dihydroxy-2-hydroxymethyl-pyrrolidine, 3,4-dihydroxy-2-hydroxymethyl-1-propylpyrrolidine, 1-butyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, 3,4-dihydroxy-2-hydroxymethyl-1-(2,2,2-trifluoroethyl)-pyrrolidine, 1-benzyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, 3,4-dihydroxy-2-hydroxymethyl-1-(2-hydroxyethyl)pyrrolidine, 3,4-dihydroxy-2-hydroxymethyl-1-(1,3-dihydroxyprop-2-yl)pyrrolidine, 3,4-dihydroxy-2-hydroxymethyl-1-(2,3-dihydroxyprop-1-yl)pyrrolidine, 1-(2-aminoethyl)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, preferably 3,4-dihydroxy-2-hydroxymethylpyrrolidine and any of the optical isomers thereof.

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21. The use according to claim 1, wherein the compound of general formula (I) is (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethyl-1-methylpyrrolidine, (2R,3R,4R)-1-cyclopropylmethyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethyl-1-propylpyrrolidine, (2R,3R,4R)-1-butyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethyl-1-(2,2,2-trifluoroethyl)-pyrrolidine, (2R,3R,4R)-1-benzyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethyl-1-(2-hydroxyethyl)pyrrolidine, (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethyl-1-(2,3-dihydroxyprop-1-yl)-pyrrolidine, (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethyl-1-(1,3-dihydroxyprop-2-yl)pyrrolidine, (2R,3R,4R)-1-(2-aminoethyl)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2S,3S,4S)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2S,3S,4S)-3,4-dihydroxy-2-hydroxymethyl-1-methylpyrrolidine, (2S,3S,4S)-1-cyclopropylmethyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2S,3S,4S)-3,4-dihydroxy-2-hydroxymethyl-1-propylpyrrolidine, (2S,3S,4S)-1-butyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2S,3S,4S)-3,4-dihydroxy-2-hydroxymethyl-1-(2,2,2-trifluoro-ethyl)pyrrolidine,

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(2S,3S,4S)-1-benzyl-3,4-dihydroxy-2-hydroxymethylpyrrolidine, (2S,3S,4S)-3,4-dihydroxy-2-hydroxymethyl-1-(2-hydroxyethyl)pyrrolidine,
(2S,3S,4S)-3,4-dihydroxy-2-hydroxymethyl-1-(2,3-dihydroxy-prop-1-yl)pyrrolidine,
(2S,3S,4S)-3,4-dihydroxy-2-hydroxymethyl-1-(1,3-dihydroxy-prop-2-yl)pyrrolidine,
5 (2S,3S,4S)-1-(2-aminoethyl)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, preferably
(2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine.

22. The use according to claim 1, wherein the compound of general formula (I) is
(2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine.

10

23. The use according to claim 1, wherein the compound of general formula (I) is
(2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, hydrobromide or (2R,3R,4R)-3,4-
dihydroxy-2-hydroxymethylpyrrolidine, hydrochloride.

15 24. (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine, hydrobromide.

25. The use of a glycogen phosphorylase inhibitor for the manufacture of a medicament for
the treatment or prophylaxis of obesity or appetite regulation.

20 26. The use of (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine for the manufacture of
a medicament for lowering of food intake.

27. The use of a glycogen phosphorylase inhibitor for the manufacture of a medicament for
lowering of food intake.

25

28. The use of (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine for the manufacture of
a medicament for lowering of food intake of food with a high fat content.

29. The use of a glycogen phosphorylase inhibitor for the manufacture of a medicament for
30 lowering of food intake of food with a high fat content.

30. The use of (2R,3R,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine for the manufacture of
a medicament for changing the preference of food with a high fat content to food with a low
fat content.

35

31. The use of a glycogen phosphorylase inhibitor for the manufacture of a medicament for changing the preference of food with a high fat content to food with a low fat content.

32. A method for the treatment or prophylaxis of obesity or appetite regulation which
5 method comprises administering an effective amount of a compound of formula I defined in anyone of the claims 1-23 to a patient in need of such a treatment.

33. A method for the treatment or prophylaxis of obesity or appetite regulation which
method comprises administering an effective amount of a glycogen phosphorylase inhibitor
10 to a patient in need of such a treatment.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00055

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/40, A61P 3/00, A61P 43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Life Sciences, Volume 39, No 7, 1986, A.M. Scofield et al, "Inhibition of mammalian digestive disaccharidases by polyhydroxy alkaloids" page 645 - page 650 --	1-33
A	WO 9709040 A1 (NOVO NORDISK A/S), 13 March 1997 (13.03.97), page 12, line 13 - line 17; page 25, line 29 - page 27, line 15; the claims	1-23,25-33
X	--	24

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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Date of the actual completion of the international search

16 May 2000

Date of mailing of the international search report

19 -05- 2000

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00055

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 9295966 A (SUNTORY LTD) 1997-11-18 (abstract) World Patents Index (online). London, U.K.: Derwent Publications, Ltd. (retrieved on 2000-05-16). Retrieved from: EPO WPI Database. DW199805, Accession no. 1998-046939; & JP 9295966 A (SUNTORY LTD) 1998-02-27 (abstract). (online) (retrieved on 2000-05-16). Retrieved from EPO PAJ Database	1-23,25-33
A	--	24
A	JP 61171465 A (FUJISAWA PHARM CO LTD) 1986-08-02 (abstract) World Patents Index (online). London, U.K.: Derwent Publications, Ltd. (retrieved on 2000-05-16). Retrieved from: EPO WPI Database. DW198643, Accession no. 1986-281039; & JP 61171465 A (FUJISAWA PHARMACEUT CO LTD) 1986-12-16 (abstract). (online) (retrieved on 2000-05-16). Retrieved from: EPO PAJ Database	1-23,25-33
X	--	24
A	GB 915456 A (C. H. BOEHRINGER SOHN), 16 January 1963 (16.01.63)	1-33
A	--	
A	STN International, File CAPLUS, CAPLUS accession no. 1991:180296, Document no. 114:180296, Simmonds, M. S. J. et al: "Behavioral and electro- physiological study of antifeedant mechanisms associated with polyhydroxy alkaloids"; & J. Chem. Ecol. (1990), 16(11), 3167-96	1-33
P,A	WO 9926659 A1 (PFIZER PRODUCTS INC.), 3 June 1999 (03.06.99), claims 1,3,6,7,13	1-33
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00055

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **32, 33**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☒ Claims Nos.: **25, 27, 29, 31, 33 (all in part)**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00055

Box I.1

Claims 32, 33 relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

Box I.2

Present claims 25, 27, 29, 31 and 33 relate to the use of a compound defined by reference to a desirable mechanism of action, namely a glycogen phosphorylase inhibitor. These claims cover the use of all compounds having this mechanism of action, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT only for use of one pyrrolidine compound, namely the compound used in claim 22. In the present case, the claims 25, 27, 29, 31 and 33 so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). Compounds can not be sufficiently defined by their mechanism of action. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has mainly been carried out for the use of pyrrolidine compounds of the general formula (I) according to claims 1-23 and the examples.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.

PCT/DK 00/00055

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9709040	A1	13/03/97	AU	6785996 A	27/03/97
				CN	1202105 A	16/12/98
				CZ	9801203 A	16/12/98
				EP	0858335 A	19/08/98
				EP	0884050 A	16/12/98
				HU	9901132 A	28/07/99
				IL	124109 D	00/00/00
				JP	11503762 T	30/03/99
				NO	982055 A	06/05/98
				US	5854272 A	29/12/98

GB	915456	A	16/01/63	FR	49 M	00/00/00

WO	9926659	A1	03/06/99	AP	9801401 D	00/00/00
				AU	9555898 A	15/06/99

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